Second, the authors excluded patients with advanced breast cancer because of the significant mortality in this group.

Third, the authors argued that exclusion of women with specific exposures is unlikely to have introduced bias. However, we are not told how many of the original study group were successfully contacted, what proportion had died, and what proportion of those recontacted, and eligible, agreed to participate in the second study. Did these proportions differ between cases and controls?

Fourth, in addition to the possibility of selection bias due to differential recruitment in the second study, the lack of a significant difference between cases and controls may be due to the restriction of the study to early stage cancer. In the study by Kabat et al. (*2*), among postmenopausal women the ratio of 2-OHE_1/16α-OHE_1 was strongly and inversely associated with breast cancer. However, this association was driven primarily by a strong association with later stage cancer (stages III and IV).

Finally, in the small sample for which the results were reported, adjustment for breast cancer risk factors (including age at menarche, age at first pregnancy, parity, family history of breast cancer, and ethnicity) was apparently not carried out. This is critical because the matched-pair design of the original study was not maintained in the current study.

We look forward to the full report, which will hopefully provide more detailed information on these questions. It should be clearly understood that these results, as they now stand, are in no way inconsistent with our hypothesis that the metabolite ratio is a valid biochemical marker for breast cancer.

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Response

Our pilot study (*1*) did not confirm Bradlow et al.'s hypothesis of an inverse association between the urinary ratio 2-OHE_1/16α-OHE_1 and breast cancer risk. Kabat and Bradlow raise a number of issues that they believe might pose problems in our study. We examine them in the order in which they were raised.

Bradlow and Kabat note that we excluded approximately 55–60% of participants in the original study. As we explicitly state in our description of our pilot study (*1*), we contacted women who had participated in a previous case–control study at our institution. For the current study, we only contacted women with early stage (< stage II) cancers. This was out of concern that the levels of the urinary metabolites might be altered by the disease in later stage patients and that any association would be the result of the disease rather than the cause of it. We also had a number of exclusion criteria that applied both to cases and to controls. We excluded cases and controls who were current smokers, who were obese, or who had recently used chemotherapy, had anesthesia, or had used other medications that could interfere with estrogen metabolism. We agree that this might limit the generalizability of the findings, but it should not result in selection bias because the criteria were applied equally to both cases and controls. These restrictions were essential because of concern that these factors could influence urinary metabolite levels and thus produce a noncausal association between the ratio of 2-OHE_1 to 16α-OHE_1 and disease.

In our pilot study publication, we provided the data for the first 25 cases and 23 controls we studied. We did not provide the participation rates/exclusion rates in each group at that time since the data collection was ongoing, so the sample in our pilot study should be regarded as a convenience sample. Further information will be provided in the full study, which will be completed shortly.

Kabat et al. (*2*) provided no information on choice of cases and controls. In their study, cases were 4 times as likely as controls to currently use alcohol and 3.8 times as likely to have a chronic condition (such as hypertension, arthritis, diabetes, asthma, glaucoma, heart disease ,and allergies); these large differences suggest that their control group may not have been an appropriate comparison group.

Bradlow and Kabat are concerned that lack of adjustment for various breast cancer risk factors would have biased our results toward the null. Although this is possible, their interpretation of their own results makes it appear unlikely. They reported that the 2-OHE_1/16α-OHE_1 ratio "did not show any consistent associations with age, race/ethnicity, age at first birth, parity, body mass index, family history of breast cancer, smoking or alcohol intake" (*2*). Bradlow and Kabat give no discussion of why the confounding would be negative. Indeed, positive confounding would appear to be equally, and possibly more, likely. In reality, it should be remembered that most of the breast cancer risk factors are relatively weak and their association with urinary metabolites would need to be rather strong to influence the associations substantively. We will evaluate all these factors as potential confounders in our full study.

Our results are, in fact, in agreement with those reported by Kabat et al. (2), who also found no association between the ratio of urinary 2-OHE_1 to 16α-OHE_1 and early stage breast cancer. As they indicate in their letter, the association they found overall was driven primarily by strong associations with later stage cancer in postmenopausal women (the same association was not found for premenopausal women). The strong association Kabat et al. (*2*) report in postmenopausal women with advanced disease may simply be an artifact of subgroup analysis, a result of the disease process itself, or the treatment their cases obtained. While it would be useful if they attempted to evaluate whether treatment or some other confounder might explain their result, in reality, it is difficult to be certain that it did not. For this reason, we excluded women with advanced disease from our study.

The 2-OHE_1 and 16α-OHE_1 assays reported in our study were conducted in the laboratory of Bradlow and colleagues at the Strang Cornell Research Laboratory, and we are indebted to him for this and for other help he gave in the execution of the study.

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